General

Guideline Title

Evidence-based guideline summary: evaluation, diagnosis, and management of congenital muscular dystrophy: report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular and Electrodiagnostic Medicine.

Bibliographic Source(s)

Kang PB, Morrison L, Iannaccone ST, Graham RJ, BÃ¶nnemann CG, Rutkowski A, Hornyak J, Wang CH, North K, Oskoui M, Getchius TS, Cox JA, Hagen EE, Gronseth G, Griggs RC. Evidence-based guideline summary: evaluation, diagnosis, and management of congenital muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular and Electrodiagnostic Medicine. Neurology. 2015 Mar 31;84(13):1369-78. [40 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- December 14, 2016 – General anesthetic and sedation drugs : The U.S. Food and Drug Administration (FDA) is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains. Consistent with animal studies, recent human studies suggest that a single, relatively short exposure to general anesthetic and sedation drugs in infants or toddlers is unlikely to have negative effects on behavior or learning. However, further research is needed to fully characterize how early life anesthetic exposure affects children's brain development.

Recommendations

Major Recommendations

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I-IV) are provided at the end of the "Major Recommendations" field.

Practice Recommendations

Given the lack of literature directly relevant to congenital muscular dystrophies (CMDs) for some of the clinical questions, some of the following recommendations are based in part on evidence from other neuromuscular disorders of childhood.

General Recommendations

Patients with CMD may develop various combinations of cardiovascular, gastrointestinal/nutritional, neurologic, ophthalmologic, orthopedic, and pulmonary manifestations. Multidisciplinary teams are recommended in the care of patients with complex neuromuscular conditions such as amyotrophic lateral sclerosis. Neuromuscular specialists, particularly child neurologists and psychiatrists with sub-specialty training, are key members of such teams, as are physicians from other specialties (e.g., cardiology, gastroenterology, neurology, ophthalmology, orthopedic surgery, pulmonology) and allied health professionals with relevant expertise (e.g., dietitians, genetic counselors, nurses, nurse practitioners, occupational therapists, physical therapists, and speech-language pathologists).

Recommendations

1. Physicians caring for children with CMD should consult a pediatric neuromuscular specialist for diagnosis and management (Level B).
2. Pediatric neuromuscular specialists should coordinate the multidisciplinary care of patients with CMD when such resources are accessible to interested families (Level B).
3. When genetic counselors are available to help families understand genetic test results and make family-planning decisions, physicians caring for patients with CMD might help families access such resources (Level B).

Use of Clinical Features, Magnetic Resonance Imaging (MRI), and Muscle Biopsy in Diagnosis

Patients with some of the classic CMD subtypes, including collagenopathies and dystroglycanopathies, have distinct phenotypic features that may help focus the diagnostic process.

Recommendation

1. Physicians should use relevant clinical features such as ethnicity and geographic location, patterns of weakness and contractures, the presence or absence of central nervous system (CNS) involvement, the timing and severity of other organ involvement, and serum creatine kinase (CK) levels to guide diagnosis in collagenopathies and in dystroglycanopathies (Level B).

Interpretation of muscle biopsy findings, especially in children, is heavily dependent on technique and the experience of the pathologist or neuromuscular specialist who interprets the studies. Proper interpretation of these studies requires knowledge of the clinical context as well as availability of advanced testing capabilities. The knowledge obtained from a muscle biopsy may help families and providers better understand the disease process affecting specific patients.

Recommendations

1. Physicians might order muscle biopsies that include immunohistochemical staining for relevant proteins in CMD cases for which the subtype-specific diagnosis is not apparent after initial diagnostic studies, if the risk associated with general anesthesia is determined to be acceptable (Level C).
2. When muscle biopsies are indicated in cases of suspected CMD, they should be performed and interpreted at centers experienced in this test modality. In some cases, optimal diagnostic information may be derived when the biopsy is performed at one center and interpreted at another (Level B).

Typical brain MRI findings of white matter abnormalities in merosinopathies can be found consistently above the age of 6 months, and the structural brain abnormalities that often accompany the dystroglycanopathies are well documented.

Muscle ultrasound and MRI studies can help distinguish neurogenic from myopathic disorders and show pathognomonic patterns for specific CMD subtypes. Muscle MRI studies likewise can help identify CMD subtypes, including collagenopathies and selenoprotein 1 (*SEPN1*)-related myopathies.

Recommendations

1. Physicians should order brain MRI scans to assist with the diagnosis of patients with clinically suspected CMD subtypes such as

merosinopathies and dystroglycanopathies, if the potential risk associated with any sedation is determined to be acceptable and if a radiologist or other physician with the appropriate expertise is available to interpret the findings (Level B).
2. Physicians might order muscle imaging studies of the lower extremities for individuals with suspected CMD subtypes such as collagenopathies (ultrasound or MRI) and *SEPN1*-related myopathy (MRI), if the risk associated with any sedation needed is determined to be acceptable and if a radiologist or other physician with the appropriate expertise is available to interpret the findings (Level C).

Genetic Diagnosis

Targeted genetic testing often identifies causative mutations in the classic CMD subtypes. However, the cost of traditional Sanger sequencing for some of the larger causative genes presents an obstacle to universal application of such sequencing, even though the testing is readily available. Genetic diagnoses are beneficial to the patient, as they often enable physicians to provide more accurate prognoses and facilitate genetic counseling and family-planning discussions, and may enable patients to become more aware of future clinical trials for which they may be eligible.

Recommendation

- When available and feasible, physicians might order targeted genetic testing for specific CMD subtypes that have well-characterized molecular causes (Level C).

This systematic review indicates that many patients with CMD do not have mutations in one of the currently known genes. The cost of next-generation sequencing (whole-exome and whole-genome sequencing) is dropping rapidly, to the point where these technologies are now readily available to many researchers who seek novel causative disease genes.

Recommendation

1. In individuals with CMD who either do not have a mutation identified in one of the commonly associated genes or have a phenotype whose genetic origins have not been well characterized, physicians might order whole-exome or whole-genome sequencing when those technologies become more accessible and affordable for routine clinical use (Level C).

Complications and Treatment

Patients with CMD experience a broad spectrum of respiratory, musculoskeletal, cognitive, and cardiac complications with variable tempo between individuals. Providers may, in appropriate circumstances, extrapolate from early-onset neuromuscular and neuromotor diseases for which consensus guidelines have been developed on the basis of both established principles of care and limited outcomes and intervention trials. There are currently no curative CMD subtype-specific interventions. Thus, all complication screening and interventions are intended to promote growth and potential development, mitigate cumulative morbidities, optimize function, and limit mortality while maximizing quality of life.

Recommendation

1. At the time of diagnosis, the physician should advise families regarding areas of uncertainty such as clinical outcomes and the value of interventions as they pertain to both longevity and quality of life. Physicians should explain the multisystem implications of neuromuscular insufficiency and guide families as they make decisions regarding the monitoring for and treatment of CMD complications (Level B).

Respiratory Complications

Patients with respiratory failure from neuromuscular-related weakness may experience conspicuous respiratory symptoms but often do not have symptoms such as dyspnea that precede the onset of respiratory failure. Noninvasive and invasive interventions are routinely utilized for children with CMD. Pulmonologists, critical care specialists, and respiratory therapists with pediatric training and experience with neuromuscular disorders are most likely to offer treatment options that optimize respiratory outcomes and minimize infection risks and complications.

Recommendations

1. Physicians should counsel families of patients with CMD that respiratory insufficiency and associated problems may be inconspicuous at the outset (Level B).
2. Physicians should monitor pulmonary function tests such as spirometry and oxygen saturation in the awake and sleep states of patients with CMD, with monitoring levels individualized on the basis of the child's clinical status (Level B).
3. Physicians should refer children with CMD to pulmonary or aerodigestive care teams, when available, that are experienced in managing the interface between oropharyngeal function, gastric reflux and dysmotility, and nutrition and respiratory systems, and can provide anticipatory guidance concerning trajectory, assessment modalities, complications, and potential interventions (Level B).

Complications from Dysphagia

Patients with neuromuscular disorders often experience dysphagia (impaired swallowing), with implications for growth and nutrition. Swallowing dysfunction may manifest as failure to thrive and may also increase the risk of admission to critical care units and mortality. Dysphagia may be diagnosed through standard multidisciplinary evaluations and radiologic studies. Safe and adequate nutrition is necessary for optimal health, and thus the potential benefits of improved nutrition with a gastrostomy must be weighed against the potential risks associated with an invasive procedure.

Recommendations

1. Neuromuscular specialists should coordinate with primary care providers to follow nutrition and growth trajectories in patients with CMD (Level B).
2. For patients with CMD, physicians should order multidisciplinary evaluations with swallow therapists, gastroenterologists, and radiologists if there is evidence of failure to thrive or respiratory symptoms (or both) (Level B).
3. For patients with CMD, a multidisciplinary care team, taking into account medical and family considerations, should recommend gastrostomy placement with or without fundoplication in the appropriate circumstances (Level B).

Cardiac Complications

Patients with CMD experience both functional and structural cardiac complications, but the frequency of these for many of the subtypes is unknown. On the basis of more extensive experience with cardiac complications in Duchenne MD and Becker MD, cardiac involvement may be subclinical and evident only on echocardiography or electrocardiography (ECG) (or both) in the earlier stages; such involvement may be amenable to pharmacologic therapy.

Recommendation

1. Physicians should refer children with CMD, regardless of subtype, for a baseline cardiac evaluation. The intervals of further evaluations should depend on the results of the baseline evaluation and the subtype-specific diagnosis (Level B).

Periprocedural Complications

Patients with neuromuscular diseases are at increased risk of periprocedural complications, including airway problems, suboptimal pain control, pulmonary complications, prolonged recovery times, and complications of bed rest and deconditioning.

Recommendations

1. Before any surgical interventions and general anesthesia in the setting of CMD, physicians should discuss the potential increased risk of complications with patients' families, because these factors may affect decision-making regarding consent to certain elective procedures (Level B).
2. When children with CMD undergo procedures involving sedation or general anesthesia, physicians should monitor longer than usual in the immediate postoperative period to diagnose and treat respiratory, nutritional, mobility, and gastrointestinal mobility complications (Level B).

Musculoskeletal Complications

Patients with CMD are at increased risk of musculoskeletal complications, including skeletal deformities and contractures. Range-of-motion exercises are straightforward interventions that generally do not involve significant risk, but the efficacy of such exercises has not been established. Data on the efficacy of bracing are also lacking for children with CMD. It is generally accepted that orthopedic surgical interventions such as heel cord–lengthening procedures relieve tendon contractures at least in the short term; however, the long-term efficacy is unclear. Neuromuscular blocking agents (e.g., botulinum toxin) can cause prolonged worsening of weakness in patients with neuromuscular diseases.

Recommendations

1. Physicians should refer to allied health professionals, including physical, occupational, and speech therapists; seating and mobility specialists; rehabilitation specialists; and orthopedic surgeons, to help maximize function and potentially slow the progression of musculoskeletal complications in children with CMD (Level B).
2. Physicians may recommend range-of-motion exercises, orthotic devices, heel cord-lengthening procedures, or a combination of these interventions for children with CMD in certain circumstances (Level B).
3. Physicians might avoid using neuromuscular blocking agents (e.g., botulinum toxin) in patients with CMD, unless the contractures are determined to cause significantly greater impairment than would any potential worsening of weakness in the targeted muscle groups (Level C).

Educational Adjustments

Before school age, children at risk of developmental delays are eligible for early intervention services as federally mandated. The Individuals with Disabilities Education Improvement Act of 2004 guarantees children with disabilities a free and appropriate public education.

Recommendation

1. Physicians should refer children with CMD to special education advocates, developmental specialists, and education specialists when appropriate for individual circumstances (Level B).

Definitions

American Academy of Neurology (AAN) Rules for Classification of Evidence for Risk of Bias

For Questions Related to Therapeutic Intervention

Class I

- Randomized, controlled clinical trial (RCT) in a representative population
- Masked or objective outcome assessment
- Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences
- Also required:
    a. Concealed allocation
    b. Primary outcome(s) clearly defined
    c. Exclusion/inclusion criteria clearly defined
    d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias
    e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
        1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority
        2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)
        3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment
        4. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers

Class II

- Cohort study meeting criteria a–e above or an RCT that lacks one or two criteria b–e
- All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences
- Masked or objective outcome assessment

Class III

- Controlled studies (including studies with external controls such as well-defined natural history controls)
- A description of major confounding differences between treatment groups that could affect outcome**
- Outcome assessment masked, objective, or performed by someone who is not a member of the treatment team

Class IV

- Did not include patients with the disease
- Did not include patients receiving different interventions
- Undefined or unaccepted interventions or outcome measures
- No measures of effectiveness or statistical precision presented or calculable

*Numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data.

For Questions Related to Screening (Yield)

Class I

- Study of a cohort of patients at risk for the outcome from a defined geographic area (i.e., population based)
- The outcome is objective
- Also required:
    a. Inclusion criteria defined
    b. At least 80% of patients undergo the screening of interest

Class II

- A non-population-based, nonclinical cohort (e.g., mailing list, volunteer panel) or a general medical, neurology clinic/center without a specialized interest in the outcome. Study meets criteria a and b (see Class I)
- The outcome is objective

Class III

- A referral cohort from a center with a potential specialized interest in the outcome

Class IV

- Did not include persons at risk for the outcome
- Did not statistically sample patients, or patients specifically selected for inclusion by outcome
- Undefined or unaccepted screening procedure or outcome measure
- No measure of frequency or statistical precision calculable

Assigning a Level of Strength to the Recommendation

When there is sufficient evidence to support an inference for the use of an intervention (i.e., the balance of benefits and harms favors the intervention), the author panel assigns one of three recommendation designations: A, B, or C. Each designation corresponds to a helping verb that denotes the level of strength of the recommendation. Level A is the strongest recommendation level and is denoted by the use of the helping verb *must*. *Must* recommendations are rare, as they are based on high confidence in the evidence and require both a high magnitude of benefit and low risk. Level B corresponds to the helping verb *should*. *Should* recommendations tend to be more common, as the requirements are less stringent but still based on the evidence and benefit–risk profile. Finally, Level C corresponds to the helping verb *may* or *might*. *May* and *might* recommendations represent the lowest allowable recommendation level the American Academy of Neurology (AAN) considers useful within the scope of clinical practice and can accommodate the highest degree of practice variation.

Level A denotes a practice recommendation that "must" be done. In almost all circumstances, adherence to the recommendation will improve health-related outcomes. A Level B indicates a recommendation that "should" be done. In most circumstances, adherence to the recommendation will likely improve health-related outcomes. A Level C represents a recommendation that "might" be done. In some circumstances, adherence to the recommendation might improve health-related outcomes.

When there is insufficient evidence to support an inference for the use of an intervention (i.e., the balance of benefits and harms is unknown) a Level U or Level R designation is appropriate.

A Level U indicates that the available evidence is insufficient to support or refute the efficacy of an intervention. A Level R is assigned when the balance of benefits and harms is unknown and the intervention is known to be expensive or have important risks. A Level R designates that the intervention should not be used outside of a research setting. Non–evidence-based factors that need to be transparently and systematically considered when formulating recommendations include the following:

- The relative value of the benefit as compared with the risk; this is derived from consideration of:
    - The importance to patients of the health related-outcomes (both benefits and harms)
    - The size of the intervention's effect
    - The risk of harm of the intervention (i.e., tolerability and safety)
- The feasibility of complying with the intervention (e.g., the intervention's availability)
- The cost of the intervention

- The expected variation in patient preferences relative to the risks, burdens, and benefits of the intervention.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Congenital muscular dystrophy (CMD)

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Neurology

Pediatrics

Intended Users

Physicians

Guideline Objective(s)

To delineate optimal diagnostic and therapeutic approaches to congenital muscular dystrophy (CMD) through a systematic review and analysis of the currently available literature

Target Population

Children with or suspected of having congenital muscular dystrophy (CMD)

Interventions and Practices Considered

General

1. Consultation with a pediatric neuromuscular specialist for diagnosis and management
2. Coordination of multidisciplinary care
3. Use of genetic counselors as a resource

Diagnosis/Evaluation

1. Use of relevant clinical features to guide diagnosis
    - Ethnicity and geographic location
    - Patterns of weakness and contractures
    - Presence or absence of central nervous system (CNS) involvement
    - Timing and severity of other organ involvement
    - Serum creatine kinase (CK) levels
2. Muscle biopsies that include immunohistochemical staining for relevant proteins
3. Brain magnetic resonance imaging (MRI) scan
4. Muscle imaging studies of the lower extremities
5. Targeted genetic testing for specific congenital muscular dystrophy (CMD) subtypes
6. Whole-exome or whole-genome sequencing

Management/Treatment

1. Advising families regarding areas of uncertainty such as clinical outcomes and the value of interventions
2. Management of respiratory complications
    - Counseling families about respiratory complications
    - Monitoring pulmonary function tests
    - Referral to pulmonary or aerodigestive care teams
3. Management of complications from dysphagia
    - Following nutrition and growth trajectories
    - Multidisciplinary evaluations with swallow therapists, gastroenterologists, and radiologists
    - Gastrostomy placement with or without fundoplication (as appropriate)
4. Referral for baseline cardiac evaluation
5. Management of periprocedural complications
    - Discussing the potential increased risk of complications with patients' families
    - Monitoring for complications in the immediate postoperative period
6. Management of musculoskeletal complications
    - Referral to physical, occupational, and speech therapists; seating and mobility specialists; rehabilitation specialists; and orthopedic surgeons
    - Range-of-motion exercises, orthotic devices, heel cord–lengthening procedures
    - Avoidance of routine use of neuromuscular blocking agents (e.g., botulinum toxin)
7. Referral of children with congenital muscular dystrophy (CMD) to special education advocates, developmental specialists, and education specialists when appropriate

Major Outcomes Considered

- Accuracy of geographic location and ethnicity, clinical features, brain imaging findings, muscle imaging findings, and muscle biopsy findings for predicting the subtype-specific diagnosis
- Accuracy of genetic testing for detecting causative mutations
- Rate of functional central nervous system, respiratory, and cardiac complications
- Feeding difficulties
- Effectiveness of treatment for complications of congenital muscular dystrophy including scoliosis and nutritional deficiencies

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The guideline panel searched the MEDLINE, EMBASE, and Scopus databases for relevant, peer-reviewed articles in humans and in all languages (see Appendix e-6 [see the "Availability of Companion Documents" field] for the full search strategy and terms). The initial search identified 2,008 abstracts. Of those, 811 articles were selected for full-text review. An updated search of MEDLINE in June 2012 and EMBASE and Scopus in August 2012 yielded an additional 1,090 articles, 70 of which were selected for review. Two panel members working independently of each other reviewed each of the 881 selected articles.

Articles were included in the review if they pertained to any of the following conditions: congenital muscular dystrophy (CMD), Ullrich disease, Bethlem myopathy, merosin deficiency, Walker–Warburg syndrome, muscle-eye-brain disease, Fukuyama CMD. Case reports were excluded. Class I, II, and III studies are discussed in the text. To target the specific treatment questions, the panel limited the search methodology to the central nervous system (CNS), myocardial dysfunction/arrhythmias, and respiratory complications (e.g., recurrent infections from presumed aspiration, hypopnea, hypoxemia, restrictive/neuromuscular insufficient lung disease).

Number of Source Documents

Seventy-eight articles were selected for inclusion in the final review.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

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    e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
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        2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)
        3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment
        4. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers

Class II

- Cohort study meeting criteria a–e above or an RCT that lacks one or two criteria b–e
- All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences
- Masked or objective outcome assessment

Class III

- Controlled studies (including studies with external controls such as well-defined natural history controls)
- A description of major confounding differences between treatment groups that could affect outcome**
- Outcome assessment masked, objective, or performed by someone who is not a member of the treatment team

Class IV

- Did not include patients with the disease
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*Numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

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For Questions Related to Screening (Yield)

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- Also required:
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    b. At least 80% of patients undergo the screening of interest

Class II

- A non-population-based, nonclinical cohort (e.g., mailing list, volunteer panel) or a general medical, neurology clinic/center without a specialized interest in the outcome. Study meets criteria a and b (see Class I)
- The outcome is objective

Class III

- A referral cohort from a center with a potential specialized interest in the outcome

Class IV

- Did not include persons at risk for the outcome
- Did not statistically sample patients, or patients specifically selected for inclusion by outcome
- Undefined or unaccepted screening procedure or outcome measure
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Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Two panel members rated each of the articles selected for review, using the 2011 American Academy of Neurology (AAN) criteria for classification of therapeutic and screening articles (see the "Rating Scheme for the Strength of the Evidence" field). Questions 1, 2, and 3 are screening questions, and question 4 is a therapeutic question. A third panel member arbitrated any differences in article ratings.

Analysis of Evidence

The panel found only a few large studies and a number of smaller studies, most likely because of the rareness of congenital muscular dystrophy (CMD) and the fact that the available studies oftentimes focus on specific subtypes. The panel decided to include at least some smaller studies so as not to miss what likely would be a significant number of valuable data, and thus set a minimum sample size of only 2 unrelated families for

inclusion and a minimum evidence level of Class III for either diagnostic or screening criteria. In the end, many of the smallest studies were excluded because they provided only low levels of evidence (Class IV); however, a small number of these studies contributed data that were not readily available in studies that were rated Class III or higher, and thus were included in the analysis.

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

This guideline was developed in accordance with the processes outlined in the 2004 and 2011 American Academy of Neurology (AAN) process manuals (see the "Availability of Companion Documents" field). In July 2010, the AAN Guideline Development Subcommittee and the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) Practice Issues Review Panel formed a panel of pediatric neurologists, a pediatric physiatrist, a pediatric critical care specialist, a patient advocate who also is a physician, and an AAN evidence-based medicine methodologist, selected to represent a range of expertise in congenital muscular dystrophies (CMDs).

The guideline panel assessed the efficacy of various screening and diagnostic procedures and therapeutic interventions for the management of patients with suspected or definite CMD. The guideline seeks to answer the following clinical questions:

1. For children with suspected CMD, how accurately do the (a) geographic location and ethnicity, (b) clinical features, (c) brain imaging findings, (d) muscle imaging findings, and (e) muscle biopsy findings predict the subtype-specific diagnosis?
2. How often does genetic testing confirm a diagnosis of CMD?
3. How often do patients with CMD experience cognitive, respiratory, and cardiac complications?
4. Are there effective treatments for complications of CMD, including scoliosis and nutritional deficiencies?

The panel formulated a rationale for recommendations based on the evidence systematically reviewed and stipulated axiomatic principles of care. This rationale is explained in a section which precedes each set of recommendations. From this rationale, the panel inferred corresponding actionable recommendations. A level of obligation was assigned to each recommendation using a modified Delphi process that considered the following prespecified domains: the confidence in the evidence systematically reviewed, the acceptability of axiomatic principles of care, the strength of indirect evidence, and the relative magnitude of benefit to harm. Additional factors explicitly considered by the panel that could modify the level of obligation include judgments regarding the importance of outcomes, cost of compliance to the recommendation relative to benefit, the availability of the intervention, and anticipated variations in patients' preferences. Appendix e-8 in the CMD Guideline (see the "Availability of Companion Documents" field) presents the prespecified rules for determining the final level of obligation from these domains. The panel indicated the level of obligation using standard modal operators. *Must* corresponds to *Level A*, very strong recommendations; *should* to *Level B*, strong recommendations; and *might* to *Level C*, weak recommendations. Appendix e-9 in the CMD Guideline indicates the panel members' judgments supporting the level of obligation for each recommendation.

Rating Scheme for the Strength of the Recommendations

Assigning a Level of Strength to the Recommendation

When there is sufficient evidence to support an inference for the use of an intervention (i.e., the balance of benefits and harms favors the intervention), the author panel assigns one of three recommendation designations: A, B, or C. Each designation corresponds to a helping verb that denotes the level of strength of the recommendation. Level A is the strongest recommendation level and is denoted by the use of the helping verb *must*. *Must* recommendations are rare, as they are based on high confidence in the evidence and require both a high magnitude of benefit and low risk. Level B corresponds to the helping verb *should*. *Should* recommendations tend to be more common, as the requirements are less stringent but still based on the evidence and benefit–risk profile. Finally, Level C corresponds to the helping verb *may* or *might*. *May* and *might* recommendations represent the lowest allowable recommendation level the American Academy of Neurology (AAN) considers useful within the scope of clinical practice and can accommodate the highest degree of practice variation.

Level A denotes a practice recommendation that "must" be done. In almost all circumstances, adherence to the recommendation will improve health-related outcomes. A Level B indicates a recommendation that "should" be done. In most circumstances, adherence to the recommendation will likely improve health-related outcomes. A Level C represents a recommendation that "might" be done. In some circumstances, adherence to the recommendation might improve health-related outcomes.

When there is insufficient evidence to support an inference for the use of an intervention (i.e., the balance of benefits and harms is unknown) a Level U or Level R designation is appropriate.

A Level U indicates that the available evidence is insufficient to support or refute the efficacy of an intervention. A Level R is assigned when the balance of benefits and harms is unknown and the intervention is known to be expensive or have important risks. A Level R designates that the intervention should not be used outside of a research setting. Non-evidence-based factors that need to be transparently and systematically considered when formulating recommendations include the following:

- The relative value of the benefit as compared with the risk; this is derived from consideration of:
  - The importance to patients of the health related-outcomes (both benefits and harms)
  - The size of the intervention's effect
  - The risk of harm of the intervention (i.e., tolerability and safety)
- The feasibility of complying with the intervention (e.g., the intervention's availability)
- The cost of the intervention
- The expected variation in patient preferences relative to the risks, burdens, and benefits of the intervention.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Drafts of the guideline have been reviewed by at least 3 American Academy of Neurology (AAN) committees, at least one American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) committee, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields.

The guideline was approved by the AAN Guideline Development Subcommittee on July 13, 2013; by the AAN Practice Committee on May 26, 2014; by the AANEM Board of Directors on December 24, 2014; and by the American Academy of Neurology Institute (AANI) Board of Directors on December 17, 2014.

This guideline was endorsed by the American Academy of Pediatrics on September 12, 2014; by the American Occupational Therapy Association on August 1, 2014; by the Child Neurology Society on July 11, 2014; and by the National Association of Neonatal Nurses on April 5, 2014.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Genetic diagnoses are beneficial to the patient, as they often enable physicians to provide more accurate prognoses and facilitate genetic

counseling and family-planning discussions, and may enable patients to become more aware of future clinical trials for which they may be eligible.
- Multiorgan system complications occur frequently; surveillance and prompt interventions are likely to be beneficial for affected children.
- See Appendix e-9 in the CMD Guideline (see the "Availability of Companion Documents" field) for clinical contextual profiles showing benefit relative to harm for each intervention.

Potential Harms

- Risk associated with any sedation
- Interpretation of muscle biopsy findings, especially in children, is heavily dependent on technique and the experience of the pathologist or neuromuscular specialist who interprets the studies. Proper interpretation of these studies requires knowledge of the clinical context as well as availability of advanced testing capabilities.
- Range-of-motion exercises are straightforward interventions that generally do not involve significant risk, but the efficacy of such exercises has not been established. Data on the efficacy of bracing are also lacking for children with congenital muscular dystrophy (CMD). It is generally accepted that orthopedic surgical interventions such as heel cord-lengthening procedures relieve tendon contractures at least in the short term; however, the long-term efficacy is unclear.
- Safe and adequate nutrition is necessary for optimal health, and thus the potential benefits of improved nutrition with a gastrostomy must be weighed against the potential risks associated with an invasive procedure.
- See Appendix e-9 in the CMD Guideline (see the "Availability of Companion Documents" field) for clinical contextual profiles showing benefit relative to harm for each intervention.

Qualifying Statements

Qualifying Statements

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Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Foreign Language Translations

Mobile Device Resources

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

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Guideline Developer(s)

American Academy of Neurology - Medical Specialty Society

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Financial Disclosures/Conflicts of Interest

Conflict of Interest

The American Academy of Neurology (AAN) and American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) are committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN and AANEM keep separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN and AANEM limit the participation of authors with substantial conflicts of interest. The AAN and AANEM forbid commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, at least one AANEM committee, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com . For complete information on this process, access the 2004 AAN process manual (see the "Availability of Companion Documents" field).

Disclosures

P. Kang has received funding for travel from the AAN, the American Academy of Pediatrics (AAP), and Sarepta Therapeutics; has received consulting fees from Third Rock Ventures, Sarepta Therapeutics, and C1 Consulting for work unrelated to continuing medical education; has received honoraria for continuing medical education lectures from the AAN, AAP, American College of Medical Genetics, and HealthmattersCME; and has received research support from the National Institute of Neurological Disorders and Stroke (NINDS) of the NIH and the Muscular Dystrophy Association (MDA). L. Morrison has received funding for travel from the AAN; currently receives funding from the NINDS/NIH and the University of New Mexico (UNM) Myotonic Dystrophy Foundation; has received support from the UNM La Tierra Sagrada Foundation; and serves as director for the pediatric MDA Clinic at UNM, for which she receives annual support. S. Iannaccone has received funding for travel from the AAN, Cure CMD, the GBS/CIDP Foundation, and NINDS/NIH; has received research support from the NINDS/NIH, Isis Pharmaceuticals, PTC Therapeutics Inc., Santhera Pharmaceuticals, and GlaxoSmithKline; and serves as director of the MDA Clinic at Children's Medical Center Dallas (for which she receives annual support) and as medical director for the Dallas MDA Summer Camp. R. Graham has served as a one-time, paid consultant for Hoffmann–La Roche Ltd. for a Pulmonary Advisory Panel on investigations pertaining to spinal muscular atrophy (SMA). C. Bönnemann has served on the scientific advisory board of Cure CMD and CMD-IR, without any compensation; has received funding for travel from BioMarin (for scientific advice, no personal compensation), Novartis (no personal compensation), and the Third Rock Ventures (no personal compensation); has served as editor-in-chief of the *Journal of Neuromuscular Disorders*; sees patients with congenital muscular dystrophy (CMD) and performs muscle ultrasound on patients with CMD; has received intramural funds from the NINDS/NIH and National Human Genome Research Institute of the NIH; and has received a research grant from MDA, PI. A. Rutkowski has received funding for clinical research from Kaiser Southern California Permanente Medical Group. J. Hornyak has received funding for travel from the AAN. C. Wang reports no disclosures relevant to the manuscript. K. North has received funding to attend a CMD workshop hosted by Cure CMD; has received clinical trials funding from PTC Therapeutics and GSK Prosensa; and has received funding from the Australian National Health and Medical Research Council (for research into congenital myopathies, dysferlin-related muscular dystrophy, and the effect of α-actinin-3 deficiency on skeletal muscle performance), from the Australia Research Council (for research into α-actinin), and from the US Army Department of Defense (for a clinical trial on lovastatin for the treatment of cognitive deficits in neurofibromatosis type 1). M. Oskoui has received funding for travel from the AAN and Isis Pharmaceuticals; has received fellowship funding from the Spinal Muscular Atrophy Foundation; has received research support from Grifols (Guillain-Barré syndrome), Isis Pharmaceuticals (SMA), and SickKids Foundation (cerebral palsy); and is a member of the Canadian Pediatric Neuromuscular Group and the Canadian Neuromuscular Disease Registry and Network. T. Getchius, J. Cox, E. Hagen, and G. Gronseth report no disclosures relevant to the manuscript. R. Griggs receives support for service on data safety monitoring boards from Novartis, PTC Therapeutics, and ViroMed; consults for Sarepta Pharmaceuticals; consults and has received research support for Marathon Pharmaceuticals and Taro Pharmaceuticals; receives royalties from Elsevier for *Cecil Textbook of Medicine* and *Cecil Essentials of Medicine*, and from Oxford University Press for *Evaluation and Treatment of Myopathies*, Second Edition; receives a stipend from the AAN for editorial work; has received grants from the NINDS/NIH, the MDA, and Parent Project for Muscular Dystrophy; and chairs the Executive Committee of the Muscle Study Group, which receives support from numerous pharmaceutical companies.

Go to Neurology.org for full disclosures.

Guideline Endorser(s)

American Academy of Pediatrics - Medical Specialty Society

American Occupational Therapy Association, Inc. - Professional Association

Child Neurology Society - Medical Specialty Society

National Association of Neonatal Nurses - Professional Association

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

A list of American Academy of Neurology (AAN) guidelines, along with a link to this guideline, is available from the AAN Web site .

Availability of Companion Documents

The following are available:

- Evidence-based guideline summary: evaluation, diagnosis, and management of congenital muscular dystrophy. Data supplement (Appendix e-6, CMD Guideline, e-references). St. Paul (MN): American Academy of Neurology; 2015. Available from the Neurology Journal Web site .
- Evaluation, diagnosis, and management of congenital muscular dystrophy. Summary of evidence-based guideline for clinicians. St. Paul (MN): American Academy of Neurology; 2015. 4 p. Available from the American Academy of Neurology (AAN) Web site .
- Evidence-based guideline summary: evaluation, diagnosis, and management of congenital muscular dystrophy: report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular and Electrodiagnostic Medicine. Slide presentation. St. Paul (MN): American Academy of Neurology; 2015. 57 p. Available from the AAN Web site .
- American Academy of Neurology (AAN). Clinical Practice Guideline Process Manual, 2011 Ed. St. Paul (MN): American Academy of Neurology. Available from the AAN Web site .
- American Academy of Neurology (AAN). Clinical Practice Guideline Process Manual, 2004 Ed. St. Paul (MN): American Academy of Neurology. Available from the AAN Web site .

In addition, a muscle disease guideline mobile application for iTunes and Google Play is available from the AAN Web site .

Patient Resources

The following is available:

- Congenital muscular dystrophy. Summary of evidence-based guideline for patients and their families. St. Paul (MN): American Academy of Neurology; 2015. 5 p. Available from the American Academy of Neurology (AAN) Web site . Also available in Spanish and Korean from the AAN Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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